REMARKS

Status of the Claims

Claims 1-41 are currently pending.

Applicants previously elected the claims of Group I (i.e., claims 1-15) in response to a restriction requirement. The Examiner states that upon reconsideration claims 1-38 will be examined together in the present application. Accordingly, claims 39-41 have been withdrawn. However, Applicants respectfully point out that claim 39 should also be examined with claims 1-38 because, like claim 38, it is directed to the amount of oligomer in the composition. Reconsideration of claim 39 is kindly requested.

Claims 1-38 stand rejected.

Claims 1, 4, 16, 31, and 32 have been amended. No new matter has been added as a result of these amendments.

Claim Objections

The Office Action objects to claim 4 because SEQ ID NOs 1 and 2 are each listed twice. In response, Applicants have amended claim 4 to delete the redundant SEQ ID Nos. Claim 32 has been similarly amended.

Response to Rejections under 35 U.S.C. §112, first Paragraph

Claims 1-38 have been rejected under 35 U.S.C. §112, first paragraph as failing to comply with the written description requirement. Applicants respectfully request reconsideration of this rejection based on the present amendments and following remarks.

The Office Action states that the claims do not recite a specific target nucleotide sequence and notes that tyrosinase is a large genus encompassing many genes. As amended, independent claims 1, 16, and 31 now specify mouse and human tyrosinase mRNA. Support for the amendments can be found throughout the application as originally filed. For instance, the Example on page 17 of the specification utilizes a mouse melanoma cell line for one aspect of assessing the effects of tyrosinase siRNA (emphasis added). Additionally, support can be found on page 7 of the specification, in paragraph 29: "...the present invention relates to the use of siRNA oligomers...and have a sequence complementary to native human tyrosinase mRNA" (emphasis added). The specific siRNA sequences disclosed on page 7 of the specification recognizes both human and mouse mRNA encoding tyrosinase. Applicants submit that the claims comply with the written description requirement, as applicants were clearly in possession of a sufficient number of representative embodiments to support the claimed genus. Withdrawal of the rejection is respectfully requested.

Claims 1-38 have also been rejected under 35 U.S.C. §112, first paragraph as failing to comply with the enablement requirement. Applicants respectfully request reconsideration of this rejection.

The Examiner argues that Applicants' *in vitro* inhibition data do not support claims directed to *in vivo* inhibition, based on the alleged unpredictability in the art. Further, the Examiner contends that "a connection between the instantly recited disorders and tyrosinase expression has not been firmly established." Applicants respectfully traverse this rejection, at least on the grounds that the Examiner has failed

to establish any unpredictability between *in vitro* and *in vivo* inhibition of tyrosinase expression, particularly with regard to the use of siRNA, and, contrary to the Examiner's assertion, the correlation between tyrosinase inhibition and treatment of hyperpigmentation disorders is very well known in the art, as discussed below.

The Office Action states that the applicant has not disclosed *in vivo* topical administration that has successfully treated the recited disorders (page 5). According to MPEP 2164.02, the initial burden is on the Examiner to give reasons for a conclusion of lack of correlation for an *in vitro* or an *in* vivo animal model example, and "[a] rigorous or an invariable exact correlation is not required." The Examiner has not provided sufficient reasons why one would not expect a correlation between the *in vitro* results provided and the *in vivo* effects of the claimed invention.

The Office Action states that the art demonstrates that attenuating or inhibiting expression of a target gene by RNA interference is unpredictable (page 5). The Examiner relies, however, on a scientific publication from 2000 (Caplen), the subject of which is not analagous to the type of RNA interference utilized by the instant invention. For example, Caplen utilized a *Drosophila* cell culture model and introduced dsRNA, which are typically >200 bp. The instant invention utilizes siRNA, which uses double-stranded RNA that typically comprises far fewer base pairs than dsRNA. For instance, as disclosed in the specification on page 7, paragraph 29, "...particularly, the present invention relates to the use of oligomers that are less than 30 oligonucleotides in length..." As explained in Caplen, there are numerous factors which influence the effectiveness of RNA interference, including the number of base pairs, which gene is targeted, the purity of the oligomers, and their concentration. The data in Caplen do not

reflect the predictability of the outcome of the instant invention as Caplen relates to much longer oigonucleotides and does not reference tyrosinase expression.

The Examiner also makes reference to a post-filing publication, Zhang, and quotes a portion of the article that indicates that delivery of siRNA to mammalian cells is not simple. However, Applicants note that Zhang, in fact, provides examples of effective delivery of siRNA to mammalian cells. Similarly, the instant specification also provides an example of effective delivery of siRNA to mammalian cells. Therefore, Applicants respectfully assert that the Examiner has not demonstrated that siRNA delivery is unpredictable. Further, Applicants fail to see how Zhang is relevant to the alleged "unpredictability of attenuating/inhibiting expression of a target gene by RNA interference" because there is no discussion whatsoever in Zhang about the correlation between *in vitro* and *in vivo* inhibition. If anything, Zhang supports the enablement of the present claims in so far as it also demonstrates effective delivery of siRNA to mammalian cells.

As to the Examiner's contention that "a connection between the instantly recited disorders and tyrosinase expression has not been firmly established" (page 4), Applicants respectfully point out that in fact, the utility of tyrosinase inhibition in treating hyperpigmentation is extremely well-known, as evidenced by the extensive patent literature disclosing various methods of inhibiting tyrosinase for this purpose. See e.g. U.S. Patent Pub. 2005/0255181, filed May 14, 2004 ("Conventionally, tyrosinase inhibitors have been used to decrease the level of melanin in the skin and thereby produce a lightly pigmented skin."); U.S. Patent Pub. 2006/0062865, filed September 17, 2004 ("Accumulation of high levels of melanin (hyperpigmentation) causes a variety

of dermatologic disorders. A number of treatments exist for these conditions and the most prominent ones function as inhibitors of tyrosinase activity."); and U.S. Patent No. 6,562,321, filed December 20, 2000 ("The prior art discloses ways to treat hyperpigmentation by application of skin lightening agents. Such agents typically lighten the skin by inhibiting the expression of tyrosinase enzymes involved in melanogenesis."). There is also an abundance of published studies from the time prior to filing of the instant application which demonstrate a link between tyrosinase and the instantly recited skin disorders. For example, Fleischer et al. (J. Am. Acad. Dermatol. 2000, vol. 42(3): 459-467) describes a clinical trial in which a tyrosinase inhibitor was used in combination with another drug to successfully treat hyperpigmentation. This paper further describes that the tyrosinase inhibitor had been used singly for some time to treat skin disorders such as hyperpigmentation.

Having established that the claimed invention inhibits tyrosinase, there is no scientific basis for the Examiner's position that Applicants have not enabled the reduction or prevention of hyperpigmentation. One skilled in the art would immediately recognize that inhibition of tyrosinase would be expected to reduce and/or prevent hyperpigmentation as tyrosinase is the rate-limiting factor in the biochemical melanin production pathway. For at least this reason, Applicants respectfully request withdrawal of this rejection.

The Examiner cites Hartmann et al. for the proposition that "therapeutic approaches are hampered by the fact that the pathophysiology of hypopigmentary disorders is still poorly understood" (emphasis added). While this may be the case, it has no relevance to Applicants' invention directed to hyperpigmentary disorders.

Clearly, hyperpigmentation is very different from hypopigmentation both in etiology and cause. In fact, Hartmann actually supports the link between tyrosinase and hyperpigmentation. Specifically, Hartmann states:

> The starting point of melanin production is tyrosine, a non-essential amino acid, which is converted by tyrosinase to dopa and dopaquinone, and subsequently to melanin. The level of tyrosinase activity directly correlates with the degree of melaninisation. Each melanocyte supplies its melanin-containing melanosomes to an average of 36 keratinocytes. The amount of supplied melanin determines the degree of cutaneous pigmentation.

Finally, the Examiner contends that the "broad genus of any tyrosinase target encompasses members of a vast family...[a]pplicant has not demonstrated that targeting such family members would result in the desired treatment effects..." (Office Action, page 5). As discussed above, the currently amended independent claims are now directed specifically to mouse and human tyrosinase mRNA. Applicants submit that nothing more than routine skill is required to practice the full scope of the claims based on the large number of representative embodiments described in the application.

In sum, Applicants respectfully submit that in view of the well-known role of tyrosinase in hyperpigmentation disorders, one skilled in the art would clearly be able to practice the instant invention using the disclosed tyrosinase expression inhibitors without undue experimentation.

For at least the above reasons, reconsideration and withdrawal of the rejections under 35 U.S.C. §112, first paragraph are respectfully requested.

CONCLUSION

Based on the foregoing amendments and remarks, applicants respectfully request reconsideration and withdrawal of the rejection of claims and allowance of this application.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. **13-4500**, Order No. 3584-4047.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **13-4500**, Order No. 3584-4047.

Respectfully submitted,
MORGAN & FINNEGAN, L.L.P.

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By: Eugene Moroz
Eugene Moroz
Registration No. 25,237

Correspondence Address:
MORGAN & FINNEGAN, L.L.P.
3 World Financial Center
New York, NY 10281-2101

(212) 415-8700 Telephone
(212) 415-8701 Facsimile